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Exploiting predisposition in the stereoselective synthesis of mono-, bi- and tetracyclic oxygen heterocycles: Equilibration between, and trapping of, alternative di- and tetraacetals

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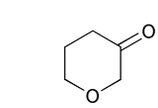
The desymmetrisation of 1,4-difuran-2-ylbutane-1,4-diol by Sharpless asymmetric oxidation gave the corresponding desymmetrised product in > 96% ee. However, the product existed as a mixture of two interconverting isomers, both of which were mixtures of anomers. The product could be trapped in high yield with a range of reagents to give stable adducts with embedded pyran-3-one, 1,6-dioxaspiro[4.5]decane or pyrano[3,2-*b*]pyran ring systems. The strategy was also applied in the interconversion between alternative tetracycles and, under acidic conditions, this process was thermodynamically controlled. The selectivity of the process was rationalised by molecular modelling using the HF/6-31G* parameter set.

Introduction

Mono- and polycyclic acetals and ethers (*e.g.* **1**–**3**) (including spirocyclic structures[1]) are 'privileged'[2] structures which are found in a wide range of natural products and interact with a diverse array of unrelated molecular targets.[3] For example, the pyrano[3,2-*b*]pyran ring system (**3**) is found in halichondrin,[4] an antitumour agent which inhibits microtubule formation, and in many polyether marine toxins.[5] Similarly, the spirocyclic ring system **2** is found in the ionophore monensin (**4**).[6] The potent serine/threonine phosphatase inhibitor okadaic acid contains both of these ring systems.[7] In these natural products, the cyclic core provides an array of hydrogen bond acceptors which can facilitate complex formation with macromolecular targets; in addition, the core acts as a well-defined molecular scaffold onto which other functional groups may be attached.



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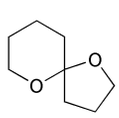

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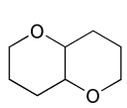

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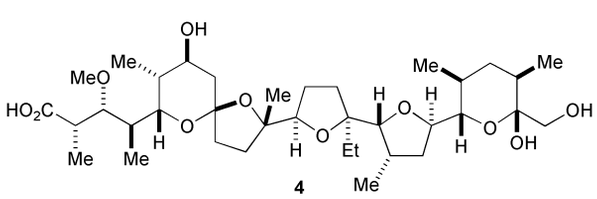

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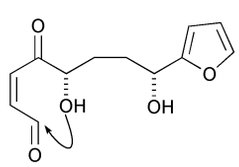
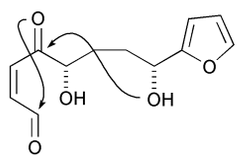
The vast majority of total syntheses of spiroacetal natural products rely on thermodynamic control to control the relative configuration of acetal stereogenic centres. In a few cases, the thermodynamically most favoured diastereoisomer of a key intermediate does not have the same relative configuration as the natural product;[8] this predicament can greatly complicate a total synthesis.

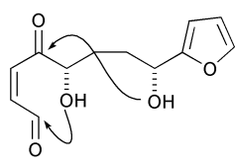
In this paper, we describe the desymmetrisation of the *meso* 1,4-diol[9,10] **15** by Sharpless asymmetric oxidation.[11,12]† The initial product of this operation is a dihydroxy keto enal (**5**) which was expected to cyclise to give an equilibrium mixture of the hemiacetals **6a**–**c** in which the pyran-3-one (**1**), 1,6-dioxaspiro[4.5]decane (**2**) and pyrano[3,2-*b*]pyran (**3**) ring systems are embedded (see Fig. 1 for possible cyclisations of **5**). Conditions are described which allow each of the hemiacetals **6a**–**c** to be trapped as stable derivatives which have potential as privileged building blocks for the synthesis of a plethora of biologically active molecules.



5 → **6a**

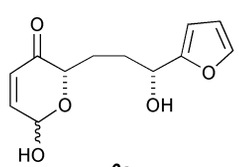


5 → **6b**

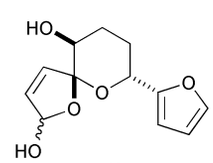


5 → **6c**

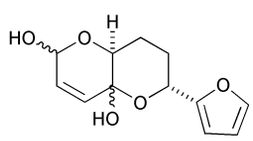
Fig. 1 Possible cyclisation pathways for the keto aldehyde **5**.



6a



6b



6c

We also describe our efforts to exploit the predisposition of more complex keto aldehydes in the synthesis of tetracyclic ring systems. Previously, three research groups have independently reported similar syntheses of a centrosymmetric tetra-THP.[14] The key step in one synthesis is shown in Scheme 1: treatment of the *meso* dione **7** with camphorsulfonic acid (CSA) and trimethylorthoformate in methanol–dichloromethane gave the tetra-THP **8** in quantitative yield.[14c] The dione **10** is, therefore, predisposed towards formation of the centrosymmetric ring system of **8** rather than the *trans*-fused ring system of **9** (see Fig. 2 for possible cyclisations of **10**).

† We have previously exploited the desymmetrisation of a derivative of **15** in the synthesis of a *C*-linked analogue of allolactose (refs. 9 and 13).

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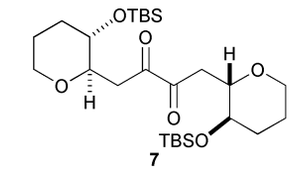
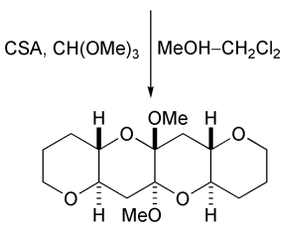
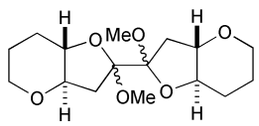




Scheme 1



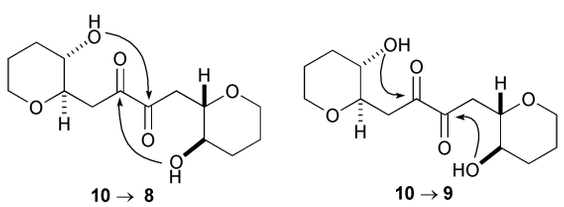


Fig. 2 Possible cyclisation pathways for the keto aldehyde **10**.

Although effective, this approach required the separate asymmetric synthesis of *both* enantiomers of a precursor which had to be subsequently combined to give the *meso* dione **7**. An alternative strategy would be to establish the relative configuration of a *meso* cyclisation precursor in a two-directional[15] fashion under substrate control. By arranging for the acetal carbons to be towards each end of the chain, it might be possible to use thermodynamic control to relay stereochemical information outwards from the 'middle' of the molecule (see Scheme 2). We have previously used this approach in the synthesis of a key intermediate in a total synthesis of Hemibrevetoxin B:[16] its particular merit is that the need to synthesise a *meso* compound from enantiomerically enriched starting materials is avoided. There are, however, at least two possible regiochemical outcomes: possibilities include cyclisation to give the centrosymmetric tetra-THP **12** or the *meso* tetraacetal **13** (see Fig. 3 for possible cyclisation pathways). In view of the precedented cyclisation **7**⟶**8**, it was hoped that the dione **11** would also cyclise to give the required centrosymmetric tetra-THP ring system (⟶**12**, Scheme 2).

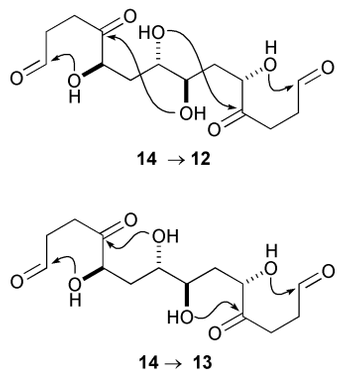


Fig. 3 Possible cyclisation pathways for the diketo dialdehyde **14**.

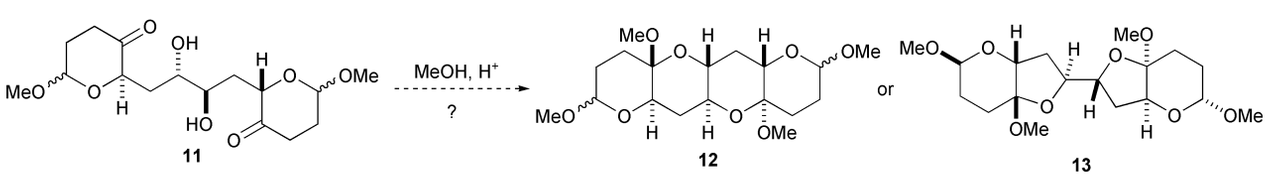
Desymmetrisation of *meso* 1,4-difuran-2-yl-butane-1,4-diol

The desymmetrisation of the *meso* 1,4-diol **15** using a Sharpless asymmetric oxidation[11,12] reaction was investigated (Scheme 3). A solution of titanium(IV) isopropoxide (1.0 eq.) and diethyl-L-tartrate (1.2 eq.) at −40 °C was added to the diol **15** in the presence of 3 Å molecular sieves, and *tert*-butyl hydroperoxide was added. After 24 h, a 79% yield of the corresponding pyranone **6** was obtained, together with a 6% yield of the doubly oxidised product[9] **16**. The characterisation of **6**, and the determination of the enantioselectivity of the desymmetrisation reaction, was complicated by its existence as a complex mixture: **6** was isolated as a 34 : 66 equilibrium mixture of the pyranone **6a** and the dihydrofuran **6b**, each of which was present as a mixture of anomers. The isolation of a mixture of **6a** and **6b** reflects the thermodynamic predisposition of the dihydroxy keto enal **5** towards the formation of the pyran-3-one (**1**) and the 1,6-dioxaspiro[4.5]decane (**2**) ring systems.

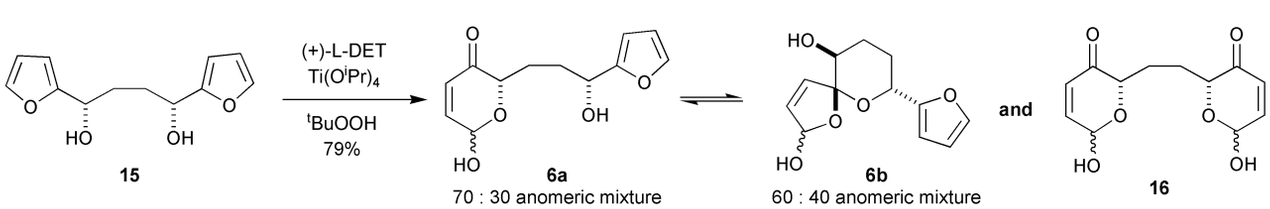
The major component of this mixture was shown to be **6b** (rather than the alternative structure **6c**) by careful analysis of its spectroscopic data: the vicinal coupling constant between the alkene protons (^3J = 5.8 Hz) and the ^{13}C chemical shifts of the hemiacetal carbons (112.1 and 110.8 ppm for the two anomers[17]) were typical[18] for five-membered rings (see Table 1).

Selective trapping of the components of the equilibrating mixture

The protection of the equilibrium mixture **6** was investigated in order to prepare stable derivatives of each of the isomers **6a**–**c**



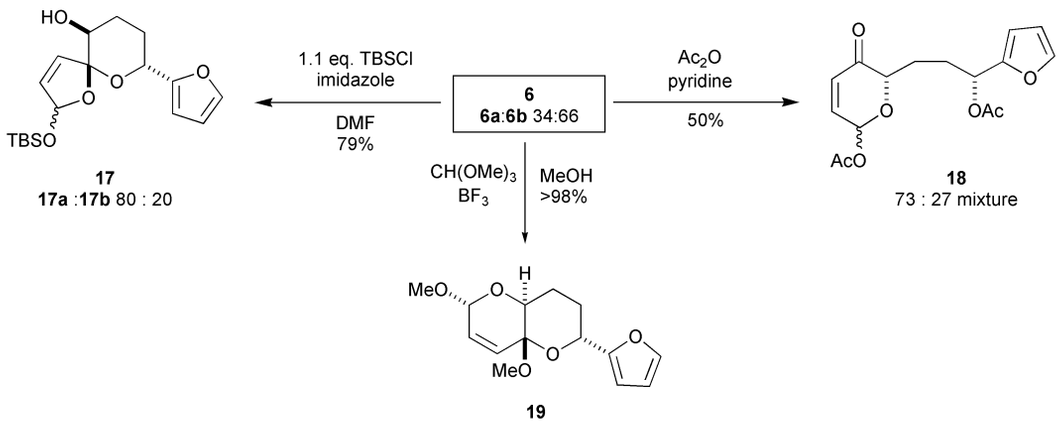
Scheme 2



Scheme 3

Table 1 Chemical shifts and coupling constants for the alkene protons H^A and H^B

	Major anomer			Minor anomer		
Compound	$\delta(H^A)$/ppm	$\delta(H^B)$/ppm	J_{AB}/Hz	$\delta(H^A)$/ppm	$\delta(H^B)$/ppm	J_{AB}/Hz
17	6.06	5.97	6.0	6.00	5.95	5.8
18	6.88	6.20	10.2	6.85	6.22	10.4
19	6.09	5.82	10.4			



Scheme 4

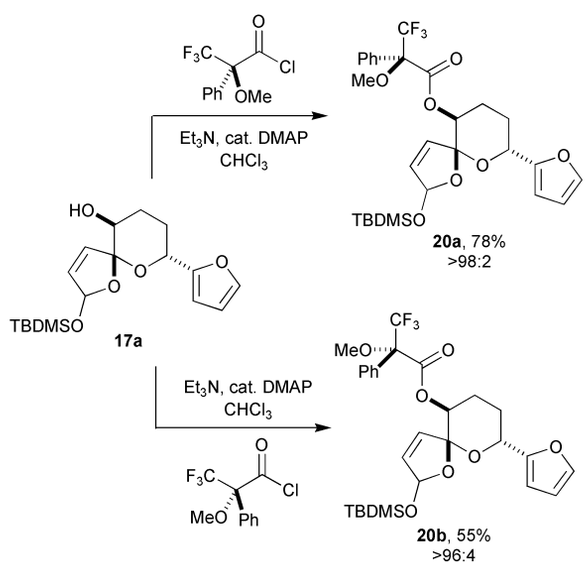
(Scheme 4). After protection of either of the hydroxyl groups in any of the isomers, the mechanism for equilibration between different ring systems would be removed.

A fruitful strategy involved reacting the hemiacetals **6** with a bulky electrophile in the hope that the least hindered hydroxyl group in the equilibrating mixture would selectively protected. Hence, reaction of the mixture **6a** and **6b** with one equivalent of *tert*-butyldimethylsilyl chloride gave an 80 : 20 anomeric mixture of dihydrofurans **17a**–**b**. This experiment reveals that, under these conditions, the hemiacetal of **6b** is the most reactive hydroxyl group present; furthermore, the isolation of a reasonably (79%) good yield of the trapped adduct indicated that the equilibration between **6a** and **6b** was fast on the timescale of reaction with the electrophile. The structures of the dihydrofurans **17** were deduced by the measurement of vicinal coupling constants (^3J = 5.8–6.6 Hz) between the alkene protons which were typical[18] of a dihydrofuran (Table 1); in addition, a doublet was observed for the remaining hydroxyl proton.

An alternative strategy involved the acetylation of the hemiacetals **6** with acetic anhydride in pyridine. Remarkably, under these conditions, the isomeric hemiacetal **6a** was trapped to give the diacetate **18** in 50% yield. The structure of **18** was deduced by measurement of the chemical shifts of, and the vicinal coupling (^3J = 10.2–10.4 Hz) between, the alkene protons (see Table 1). Once more, the yield of the product obtained indicated that equilibration between the isomers **6a** and **6b** was faster than the trapping reaction.

Determination of the enantioselectivity of the desymmetrisation reaction

The enantioselectivity of the desymmetrisation reaction **15**⟶**6** was determined by conversion of the major anomer **17a** into the corresponding Mosher's esters (Scheme 5).[19] Hence, acylation of **17a** with (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)-phenyl acetyl chloride gave the corresponding (*R*)- and (*S*)-Mosher's esters **20a** and **20b** as > 98 : 2 and > 96 : 4 mixtures of diastereoisomers respectively. Since the product formed from the major enantiomer in each reaction is the same diastereoisomer as would have been formed from the minor enantiomer in the other, we were able to determine a lower limit for the enantiomeric excess of **17a**: we estimate that **17a**, and hence **6**, had > 96% ee.

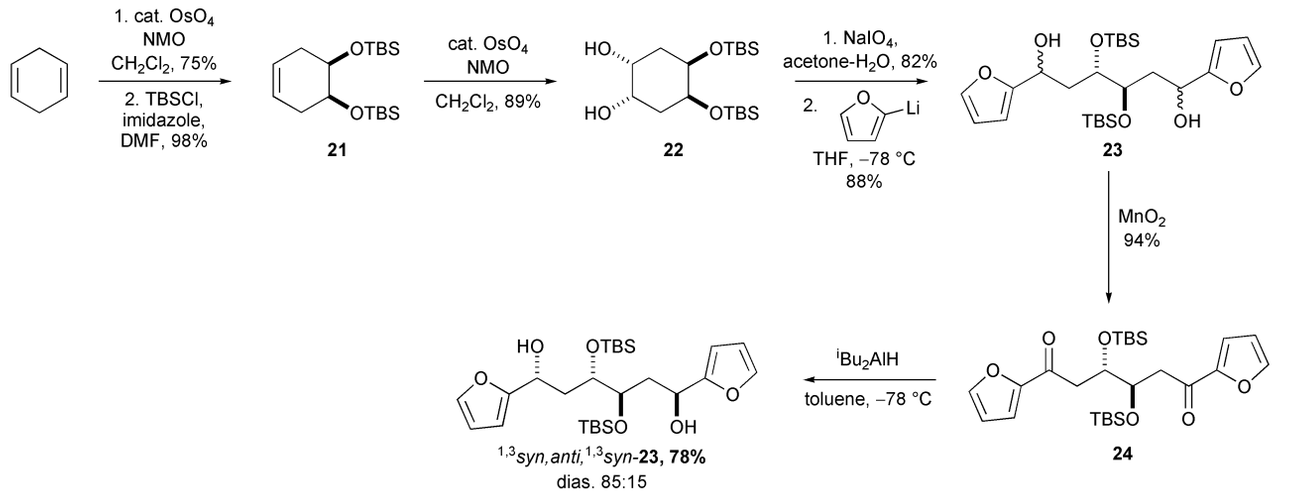


Scheme 5

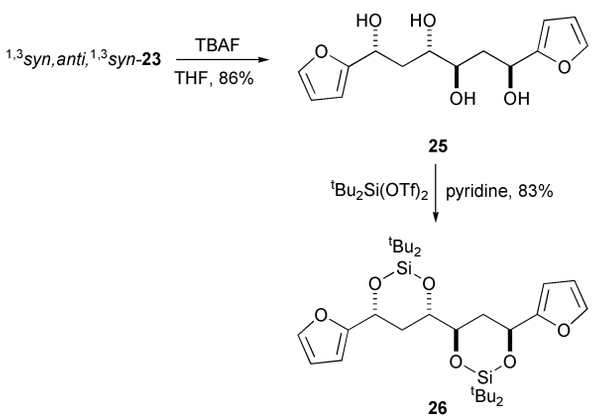
The determination of the absolute configuration of functionalised alcohols by analysis of the ^1H or ^{19}F NMR spectra of the corresponding arylmethoxyacetate derivatives is notoriously unreliable.[20] Instead, we have assigned the absolute configuration of the products, **6**, of our desymmetrisation reaction by correlation with the sense of asymmetry observed in the kinetic resolution of 2-furyl alcohols.[12]

Two-directional synthesis of a *meso* cyclisation precursor using substrate control

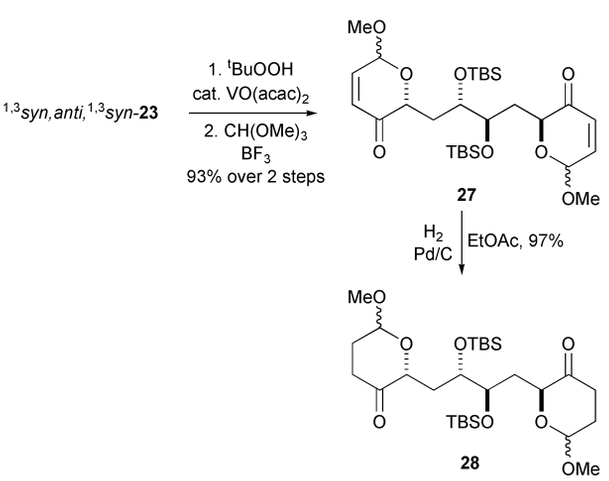
The *meso* cyclisation precursor **28**, a masked version of the diketo dialdehyde **14**, was prepared by two-directional elaboration under substrate control (see Schemes 6 and 8). Dihydroxylation of 1,4-cyclohexadiene under Upjohn's conditions,[21] and silylation, gave the protected diol **21** (Scheme 6). The remaining double bond of **21** was dihydroxylated to give the diol **22** as a single diastereoisomer in 89% yield.[22] Cleavage of the cyclohexane ring of **22** with sodium periodate gave a dialdehyde[22] which was immediately treated with an excess of 2-lithio furan at −78 °C in THF; the diol **23** was obtained as a mixture of diastereoisomers.



Scheme 6



Scheme 7



Scheme 8

In order to control its relative configuration, the diol **23** was oxidised to the corresponding dione **24** using activated manganese dioxide. No reaction was observed with barium manganate,[23] pyridinium dichromate[24] or catalytic TPAP (25 mol%) and NMO.[25] Treatment of the dione **24** with DIBAL at −78 °C in toluene gave the diol **23** (92% yield) as an 85 : 15 mixture of diastereoisomers from which the ^{1,3}*syn*,*anti*,^{1,3}*syn* isomer was obtained in 78% yield.[10] The relative configuration of the diol ^{1,3}*syn*,*anti*,^{1,3}*syn*-**23** was confirmed by conversion into the cyclic derivative **26**; hence, treatment with TBAF gave the tetraol **25** which was converted into the bis(di-*tert*-butylsilylene) derivative **26** (Scheme 7).[26] The ^{1,3}*syn* configuration of **26** was confirmed by careful analysis of its 500 MHz ^{1}H NMR spectrum.[10]

Treatment of the difuryl diol ^{1,3}*syn*,*anti*,^{1,3}*syn*-**23** with *tert*-butyl hydroperoxide and catalytic vanadyl acetylacetonate resulted in double oxidative ring expansion;[27] protection gave the dipyranone **27** as a 61 : 39 mixture of anomers (Scheme 8). Hydrogenation of **27**, using palladium on charcoal catalyst, proceeded efficiently to give the diacetal **28** in 97% yield.

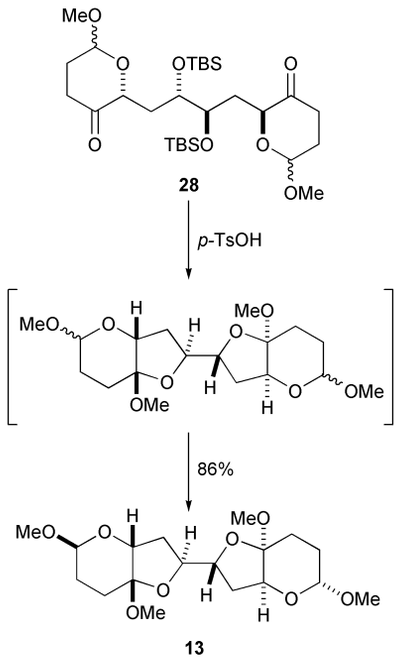
Synthesis of bi- and tetra-cyclic polyethers by equilibration between alternative di- and tetraacetals

The hemiacetals **6** were converted into the most stable arrangement of the corresponding acetals. Hence, treatment of the mixture of **6a** and **6b** with trimethylorthoformate and boron trifluoride etherate in methanol gave a quantitative yield of the diacetal **19** (Scheme 4). Presumably, the formation of the bicyclic structure reflects the thermodynamic stability of **19** under the conditions of the reaction: although the corresponding hemiacetal **6c** is not present (< 2%) in the starting material, the high concentration of methanol makes the incorporation of the two methoxy groups, and hence the formation of **19**, favourable.

The predisposition of the diketo dialdehyde **14** towards the formation of particular polyether ring systems was investigated by deprotection of its masked derivative **28** (Scheme 9). Treatment of **28** with *p*-toluenesulfonic acid in methanol resulted in the clean removal of the *tert*-butyldimethylsilyl protecting groups and cyclisation. Initially, the product obtained was a mixture of anomers; however, after stirring at room temperature for 72 h, the two 'outer' acetal centres underwent equilibration to give the *meso* tetracyclic tetraacetal **13** as a single diastereoisomer. The relative configuration of **13** was determined by X-ray crystallographic analysis ‡, which also confirmed the formation of the two central THF rings and the *cis* ring fusion between the THF and THP rings (Fig. 4). The methoxy groups were found to have adopted axial positions on the THP rings to maximise anomeric stabilisation.[28] Furthermore, the tetraacetal **13** was found to adopt a centrosymmetric conformation in order to minimise the unfavourable gauche interactions which would be encountered by rotation around the central bond.

In order to help distinguish between kinetic and thermodynamic factors, the cyclisation was investigated under different reaction conditions. Hence, treatment of **28** with TBAF in THF gave a complex mixture of products; however, virtually all of this mixture was converted into the *meso* tetraacetal **13** by treatment with *p*-toluenesulfonic acid in methanol. Furthermore, subjection of the *meso* tetraacetal **13** to harsher reaction

‡ CCDC reference number 20673. See http://www.rsc.org/suppdata/ob/b3/b303089j/ for crystallographic data in .cif or other electronic format.



Scheme 9

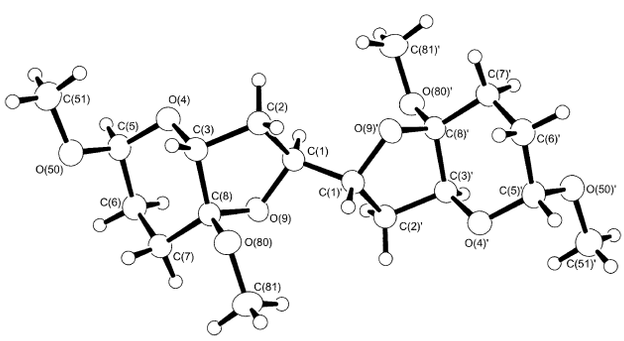
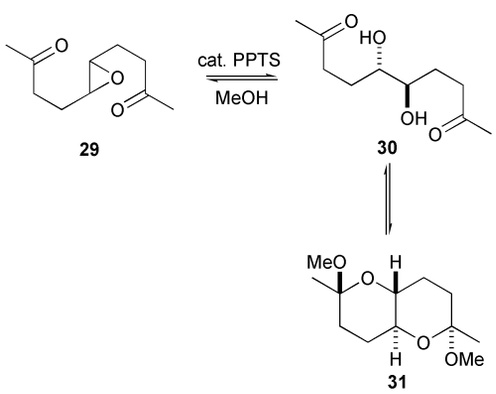


Fig. 4 X-Ray crystal structure of the tetraacetal **13**.

conditions (treatment with two equivalents of *p*-toluenesulfonic acid in methanol for either two weeks at room temperature or for three days at reflux) did not change the composition of the reaction mixture.

All of these results suggest that the tetraacetal **13**, and not the centrosymmetric tetra-THP **12**, is the thermodynamically most favourable isomer. In some respects, this result is surprising, since we have shown that two analogues of the dihydroxy diketo dialdehyde **14** are predisposed towards the formation of *trans*-fused di-THP structures. First, the dihydroxy dione **30**, a model for the central portion of **14**, is predisposed towards formation of the di-THP **31** (which would correspond to the central two THP rings of **12**) (Scheme 10).[16] Alternative cyclisation modes of the dihydroxy dione **30** are summarised in Fig. 5.



Scheme 10

Table 2 HF/6-31G* estimated energies for the tetracetals **12** and **13**

Entry	Isomer	E_{rel}/kJ mol^{-1}	Equilibrium distribution[a](%)
1	**13**	0.0	99.9
2	**12**	16.2	0.1

[a] Ratios are estimated at 300 K.

Table 3 HF/6-31G* estimated energies for the diacetals **31** and **32a–c**

Entry	Isomer	E_{rel}/kJ mol^{-1}	Equilibrium distribution[a](%)
1	**31**	0.0	96.7
2	**32a**	11.2	1.0
3	**32b**[b]	10.8	2.3
4	**32c**	26.5	0.0

[a] Ratios are estimated at 300 K. [b] This isomer has a degenerate enantiomeric isomer.

In addition, the keto aldehyde **5**, which may be considered to be a crude model of one half of the diketo dialdehyde **14**, also cyclises to give a *trans*-fused di-THP (corresponding to the 'left-hand' two THP rings of **12**) (see **6**⟶**19**; Scheme 4).

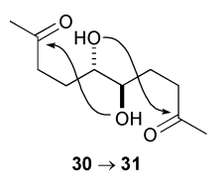
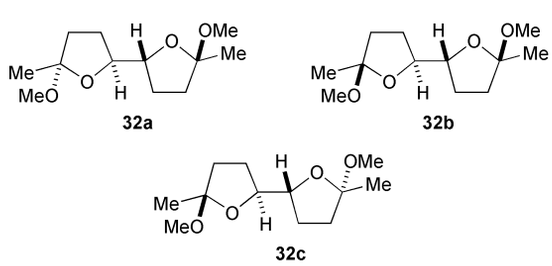


Fig. 5 Cyclisation pathways of the dihydroxy dione **30**.

Previously, Dominey and Goodman have urged that care be taken when attempting to use theoretical calculations to estimate the position of equilibria in competitive acetal formations: MM2* was found to poorly predict the position of equilibria between five- and six-membered acetals.[29] We have estimated the heats of formation of alternative and tetraacetal products (**12** and **13**) using *ab initio* methods. These calculations predict gas-phase structures, and are therefore more reliable when modelling experimental results conducted in non-polar solvents (methanol has dielectric constant, $\varepsilon = 32.6$,[30] at 298 K); furthermore, entropic effects are ignored.

The ground state conformation of **13** predicted using the HF/6-31G* parameter set was remarkably similar to the experimentally determined X-ray crystal structure (Fig. 4): the molecule was predicted to adopt a centrosymmetric conformation and the Me–O bonds were predicted to stagger the correct bonds. The experimentally observed *meso* tetraacetal **13** was predicted to be 16 kJ mol^{-1} more stable than the alternative isomer **12** (Table 2). This energy difference suggests that, at equilibrium at room temperature, 99.9% of the sample would populate this arrangement. Indeed, the estimated energy difference between **12** and **13** is sufficiently large that, even allowing for a large error and the inability to account for solvent and entropic effects, the tetraacetal **13** would be expected to be the thermodynamically most stable isomer.

In order to validate the approach, we have also rationalised the position of equilibrium between the bicyclic di-THP **31** and its regioisomeric alternatives **32a–c** (Table 3). The calculations



correctly predicted that the di-THP **31** is the thermodynamically most stable isomer. In our experimental study, we found that only the di-THP (isolated in 85% yield) was observed at equilibrium at room temperature. The rationalisation of the outcome of two rather different acetal equilibria lends support to the use of the HF/6-31G* parameter set to predict of position of equilibrium in related systems.

Conclusion

Equilibria involving di- and tetraacetals can lead to a wide range of complex polycyclic heterocyclic structures. Unsurprisingly, hydroxylated di- and tetracarbonyl compounds may be predisposed towards the stereo- and regiocontrolled formation of specific polycyclic ring systems. The particular fate of the diketone **28**, a protected version of the dihydroxy diketo dialdehyde **14**, stemmed from cyclisation possibilities which were unavailable to the related diketone **7** (see Schemes 1, 2 and 9). The substituents on each of the THP rings of **7** had a *trans* relationship, which forced any polycyclic products to have *trans* ring fusions to these 'outside' rings (as in **8** and **9**). This restriction is not placed on the diketone **28**: with the possibility of a *cis* ring fusion in the polycyclic products, the formation of the tetracyclic tetraacetal **13** became favourable. Although the synthesis of a centrosymmetric tetra-THP was not possible in this case, thermodynamic control was used to induce the stereoselective formation of four new stereogenic centres (**28**⟶**13**). Furthermore, the synthesis of a complex *meso* polycyclic ring system was possible without having to combine two enantiomeric precursors.

The exploitation of acetal equilibria in synthesis is not, however, necessarily restricted to reactions which proceed under thermodynamic control. For example, the desymmetrisation of the *meso* diol[10] **15** by Sharpless asymmetric oxidation was highly enantioselective, yielding products with > 96% ee, and the product existed as a mixture of pyranone (**6a**) and 1,6-dioxaspiro[4.5]decane (**6b**) isomers. Remarkably, it was possible to react the mixture of isomers **6a/6b** under different reaction conditions to give stable adducts in which a 1,6-dioxaspiro-[4.5]decane (**17**), a pyran-3-one (**18**) or a pyrano[3,2-*b*]pyran (**19**) ring system had been trapped in high yield. These compounds have potential as highly functionalised templates for the synthesis of a wide variety of mono- and bicyclic polyethers.

Experimental

General experimental methods have been previously described.[31] Coupling constants are given in Hz. Optical rotations are given in 10^{-1} deg cm^2 g^{-1}. Computation modelling experiments were carried out using Spartan software and the Gaussian 98 package.[32] Starting points for geometry optimisation were generated from a conformational search using the Spartan software and an MMF force field. Minimum energy geometries for each isomer were then estimated using Spartan software with both the force field MM2* and semi-empirical AM1 methods. Minimum energy geometries for each isomer were then reoptimised in the Gaussian 98 package at the HF/6-31G* level of theory. Geometries were optimised using very tight convergence criteria; the GD11S algorithm was used to force convergence if default optimisation methods failed to find a stationary point.

Equilibrium mixture of (2*S*)-2-[(*R*)-3′-furan-2-yl-3′-hydroxypropyl]-6-hydroxy-6*H*-pyran-3-one 6a and (5*S*,7*R*,10*S*)-7-furan-2-yl-1,6-dioxaspiro[4.5]dec-3-ene-2,10-diol 6b

Titanium(IV) isopropoxide (594 μl, 2.00 mmol) was added to a solution of diethyl-L-tartrate (410 μl, 2.40 mmol) in dichloromethane (30 ml) and the mixture was stirred for 20 minutes under nitrogen at −40 °C. This mixture was added to a stirred solution of the diol **15** (444 mg, 2.00 mmol) and molecular sieves 3 Å (1.0 g) in dichloromethane (20 ml) and stirred for 20 minutes under nitrogen at −40 °C. *tert*-Butyl hydroperoxide (1.10 ml of a 5 M solution in decane, 2.20 mmol) was added and the reaction mixture was stirred for 24 hours under nitrogen at −40 °C. The reaction mixture was quenched with water (50 ml), the organic layer and fine precipitate was removed *via* syringe and the aqueous layer extracted with dichloromethane (3 × 20 ml). The combined organic extracts were filtered and the insoluble residue washed with chloroform (1 ml), to give the dipyranone **16** (14 mg, 6%) as a colourless powder, spectroscopically identical to that obtained previously.[9] The organic filtrate was dried ($MgSO_4$), evaporated under reduced pressure, pre-absorbed onto silica gel and purified by flash chromatography, eluting with 6 : 4 EtOAc–petrol, to give the monopyranone **6** (376 mg, 79%) as a colourless viscous oil, R_f 0.25 (3 : 2 EtOAc–petrol); (Found: MNa^+ 261.0740; $C_{12}H_{14}O_5$ requires *MNa*, 261.0739); $[a]_D$ +191.2 (*c* 0.1 in $CHCl_3$; > 95% ee); ν_{max}/cm^{-1} ($CHCl_3$ solution) 3300 (OH), 3000–2850 and 1630 (C=O); δ_H (500 MHz; $CDCl_3$) 7.36 (2.8H, m, furan H-5), 6.92 (0.10H, dd, *J* = 10.3 and 1.5, H-5^{6a,min}), 6.88 (0.24H, dd, *J* = 10.3 and 3.4, H-5^{6a,maj}), 6.30 (2.0H, m, furan H-4 and H-3), 6.16 (0.66H, m, H-2^{6b,maj} and H-3^{6b,min}), 6.13 (0.10H, m, H-4^{6a,min}), 6.08 (0.64H, m, H-3^{6b,maj} and H-4^{6a,maj}), 6.03 (0.26H, d, *J* = 5.8, H-4^{6b,min}), 5.94 (0.66H, m, H-4^{6b,maj} and H-2^{6b,min}), 5.62 (0.34H, d, *J* = 3.2, H-6^{6a}), 5.02 (0.26H, dd, *J* = 11.8 and 2.4, H-7^{6b,min}), 4.98 (0.40H, dd, *J* = 11.8 and 2.6, H-7^{6b,maj}), 4.74 (0.34H, m, H-2^{6a}), 4.65 (0.24H, dd, *J* = 7.9 and 3.9, H-3′^{6a,maj}), 4.30 (0.26H, m, OH^{6b,min}), 4.17 (0.40H, m, OH^{6b,maj}), 4.14 (0.10H, dd, *J* = 7.9 and 3.0, H-3′^{6a,min}), 3.90 (0.34H, m, OH$^{6a,maj+min}$), 3.77 (0.26H, dd, *J* = 11.3 and 4.7, H-10^{6b,min}), 3.73 (0.40H, dd, *J* = 11.54 and 4.7, H-10^{6b,maj}), 3.00–2.30 (1.0H, m, OH), 2.20–1.85 (4.0H, m, CH_2CH_2); δ_C (125 MHz; $CDCl_3$) 196.3 (C=O^{6a}), 195.9 (C=O^{6a}), 156.3 (C-2 furan,$^{6a,maj+min}$), 153.5 (C-2 furan,^{6b}), 153.4 (C-2 furan^{6b}), 148.1 (C-5^{6a,min}), 144.7 (C-5^{6a,maj}), 142.5, 142.4, 142.3 and 142.0 (C-5 furan), 133.5 (C-3^{6b,min}), 133.3 (C-3^{6b,maj}), 132.7 (C-4^{6b,min}), 132.5 (C-4^{6b,maj}), 128.5 (C-5^{6a,min}), 127.4 (C-5^{6a,maj}), 112.1 (C-5^{6b,maj}), 110.8 (C-5^{6b,min}), 110.2, 110.1, 107.5, 107.3 and 106.1 (C-3 and C-4 furan), 103.2 (C-2^{6b,min}), 102.7 (C-2^{6b,maj}), 90.8 (C-6^{6a,min}), 87.6 (C-6^{6a,maj}), 78.6 (C-2^{6a,min}), 73.6 (C-2^{6a,maj}), 68.7 (C-10^{6b,min}), 67.9 (C-10^{6b,maj}), 67.6, 67.5, 67.5 and 67.4 (C-7$^{6b,maj+min}$ and C-3′$^{6a,maj+min}$), 31.1, 30.8, 29.7, 28.8, 28.8, 28.8, 28.5, 26.7 and 25.5 ($CH_2^{6a,6b}$); *m*/*z* (ES) 261 (MNa^+, 100%). Analysis of the product by 500 MHz ^{1}H NMR spectroscopy revealed it to be a 66 : 34 mixture of the *dihydrofuran* **6b** (60 : 40 mixture of anomers) and the *pyranone* **6a** (70 : 30 mixture of anomers).

(5*S*,7*R*,10*S*)-2-(*tert*-Butyldimethylsilanyloxy)-7-furan-2-yl-1,6-dioxaspiro[4.5]dec-3-ene-10-ol 17

The desymmetrised product **6** (109.3 mg, 0.459 mmol), *tert*-butyldimethylsilyl chloride (76.3 mg, 0.505 mmol) and imidazole (47 mg, 0.689 mmol) were stirred under nitrogen at room temperature in DMF (0.7 ml) for 29 hours. The reaction mixture was diluted with chloroform (15 ml) and washed with water (5 × 10 ml). The organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude product. Analysis by 300 MHz ^{1}H NMR spectroscopy revealed an 80 : 20 mixture of diastereoisomers. The crude product was pre-absorbed onto silica gel and purified by flash chromatography, eluting with 7 : 3 petrol–EtOAc, to give the *silyl ether* **17a** (93 mg, 63%) as a colourless oil, R_f 0.3 (7 : 3 petrol–EtOAc); (Found: MH^+ 353.1783; $C_{18}H_{28}O_5Si$ requires *MH*, 353.1784); $[a]_D$ −6.4 (*c* 0.1 in $CHCl_3$; > 95% ee); ν_{max}/cm^{-1} ($CHCl_3$ solution) 3400 (OH), 2930 (CH) and 1690 (C=C); δ_H (500 MHz; $CDCl_3$) 7.34 (1H, dd, *J* = 1.8 and 0.8, H-5 furan), 6.29 (1H, dd, *J* = 3.2 and 1.8, H-4 furan), 6.23 (1H, d, *J* = 3.2, H-3 furan), 6.06 (2H, m, H-2 and H-3), 5.97 (1H, dd, *J* = 6.0 and 1.2, H-4), 4.95 (1H, dd, *J* = 11.7 and 2.3, H-7), 3.76 (1H, ddd, *J* = 11.6, 10.1

and 4.6, H-10), 2.10 (2H, m, H-8 and H-9), 1.96 (1H, m, H-8), 1.85 (1H, m, H-9), 1.47 (1H, d, J = 10.1, OH), 0.94 (9H, s, ^{t}Bu), 0.21 (3H, s, SiMe), 0.19 (3H, s, SiMe); δ_C (125 MHz; $CDCl_3$) 153.7 (C-2 furan), 142.3 (C-5 furan), 134.0 (C-3), 131.4 (C-4), 111.2 (C-5), 110.0 (C-4 furan), 107.2 (C-3 furan), 103.1 (C-2), 68.9 (C-10), 67.3 (C-7), 29.2 and 28.9 (C-8 and C-9), 25.7 (^{t}Bu), 18.0 (^{t}Bu), −4.1 (SiMe), −4.7 (SiMe); m/z (ES) 353 (MH^+, 100%). Integration of the 500 MHz ^{1}H NMR spectrum of the (*R*)- and (*S*)-Mosher's esters of this material showed it to have > 96% ee.

Also obtained was the *silyl ether* **17b** (23 mg, 16%) as a colourless oil, R_f 0.25 (7 : 3 petrol–EtOAc); (Found: MH^+ 353.1782; $C_{18}H_{28}O_5Si$ requires *MH*, 353.1784); $[\alpha]_D$ −4.0 (*c* 0.1 in $CHCl_3$; >95% ee); ν_{max}/cm^{-1} ($CHCl_3$ solution) 3401.05 (OH), 2930 (CH), 1634 (C=C), 1473, 1255, 1072 and 1012; δ_H (500 MHz; $CDCl_3$) 7.37 (1H, dd, J = 1.9 and 0.9, H-5 furan), 6.32 (1H, dd, J = 3.2 and 1.9, H-4 furan), 6.29 (1H, d, J = 3.4, H-3 furan), 6.24 (1H, m, H-2), 6.00 (1H, dd, J = 5.8 and 0.9, H-3), 5.95 (1H, dd, J = 5.8 and 0.9, H-4), 4.96 (1H, dd, J = 11.9 and 2.6, H-7), 3.67 (1H, td, J = 11.1 and 4.9, H-10), 2.47 (1H, d, J = 10.9, OH), 2.13 (1H, m, H-9^{eq}), 2.05 (1H, m, H-8^{ax}), 1.96 (1H, m, H-8^{eq}), 1.80 (1H, m, H-9^{ax}), 0.93 (9H, s, ^{t}Bu), 0.21 (3H, s, SiMe) and 0.19 (3H, s, SiMe); δ_C (125 MHz; $CDCl_3$) 153.8 (C-2 furan), 153.2 (C-3), 142.4 (C-5 furan), 131.9 (C-4), 113.0 (C-5), 110.1 (C-4 furan), 107.2 (C-3 furan), 102.4 (C-2), 67.8 (C-7), 67.8 (C-10), 29.3 and 28.8 (C-8 and C-9), 25.6 (^{t}Bu), 17.9 (^{t}Bu), −4.3 (SiMe) and −4.9 (SiMe); m/z (ES) 353 (MH^+, 100%).

Acetic acid (*R*)-3′-[(2*S*)-6-acetoxy-3-oxo-3,6-dihydro-2*H*-pyran-2-yl]-1′-furan-2-yl-propyl ester 18

Acetic anhydride (2 ml, 9.35 mmol) was added to a stirred solution of the desymmetrised product **6** (1.70 g, 4.97 mmol) in pyridine (20 ml) and the reaction mixture was stirred for 24 hours under nitrogen at room temperature. The reaction mixture was evaporated under reduced pressure to give a crude product which was purified by flash chromatography, eluting with 2 : 8 EtOAc–petrol to give the *diacetate* **18** (1.49 g, 50%; 73 : 27 anomeric mixture) as a yellow oil, R_f 0.77 (6 : 4 EtOAc–petrol); (Found: MNa^+ 345.0945; $C_{16}H_{18}O_7$ requires *MNa*, 345.0950); $[\alpha]_D$ +5.89 (*c* 1.23 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ solution) 2941.6 (CH), 1742.49 (C=O ester), 1697.86 (C=O enone), 1438.32, 1373.35 and 1236.33; δ_H (500 MHz; $CDCl_3$) 7.38 (1.7H, m, H-5 furan), 6.88 (1H, dd, J = 10.2 and 3.7, H-5^{maj}), 6.85 (0.4H, dd, J = 10.4 and 2.6, H-5^{min}), 6.54 (0.4H, dd, J = 2.6 and 1.3, H-6^{min}), 6.50 (1H, d, J = 3.7, H-6^{maj}), 6.34–6.28 (3.7H, m, H-3 furan$^{maj+min}$ and H-4 furan$^{maj+min}$), 6.22 (0.4H, dd, J = 10.4 and 1.3, H-4^{min}), 6.20 (1H, dd, J = 10.2 and 0.4, H-4^{maj}), 5.84 (1.4H, t, J = 7.2, H-1′), 4.50 (1H, dd, J = 7.7 and 3.9, H-2^{maj}), 4.24 (1H, m, H-2^{min}), 2.2–2.0 (14H, m, H-3′$^{min+maj}$, H-2′$^{min+maj}$ and Me$^{maj+min}$); δ_C (125 MHz; $CDCl_3$) 195.0 and 194.9 (C=O enone$^{maj+min}$), 170.4 (C=O ester^{min}), 170.2 (C=O ester^{maj}), 170.1 (C=O ester^{min}), 169.5 (C=O ester^{maj}), 153.1 (C-2 furan^{min}), 152.2 (C-2 furan^{maj}), 143.3 (C-5^{min}), 142.6 and 142.5 (C-5 furan$^{maj+min}$), 141.7 (C-5^{maj}), 128.6 and 128.5 (C-4$^{maj+min}$), 110.3, 110.2, 110.2 and 108.7 (C-3 furan$^{maj+min}$ and C-4 furan$^{maj+min}$), 87.8 (C-6^{min}), 87.0 (C-6^{maj}), 79.1 (C-2^{min}), 75.2 (C-2^{maj}), 68.4 and 68.3 (C-1′$^{maj+min}$), 28.6, 27.8, 25.6 and 24.9 (C-3′$^{maj+min}$ and C-2′$^{maj+min}$), 21.1 (Me^{maj}), 21.1 (Me^{min}), 21.0 (Me^{min}) and 21.0 (Me^{maj}); m/z (ES) 345 (MNa^+, 100%).

(2*R*,4a*S*,6*R*,8a*R*)-2-Furan-2-yl-6,8a-dimethoxy-2,3,4,4a,6,8a-hexahydropyrano[3,2-*b*]pyran 19

Boron trifluoride diethyletherate complex (50 µl, 0.4 mmol) was added slowly to a stirred solution of the desymmetrised product **6** (95 mg, 0.4 mmol) and trimethyl orthoformate (109 µl, 1.0 mmol) in methanol (2 ml) at room temperature. The solution was stirred for a further 2 h before quenching with a saturated aqueous solution of sodium bicarbonate (2 ml). Excess solvent was removed under reduced pressure and the aqueous layer extracted with chloroform (3 × 5 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (2 × 5 ml) and then with brine (5 ml). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product which was purified by flash chromatography (gradient elution: 15 : 85⟶2 : 8 petrol–EtOAc) gave the diacetal **19** (103 mg, > 98%) as a colourless oil, R_f 0.52 (20 : 80 EtOAc–petrol); (Found: MH^+ 267.1233; $C_{14}H_{18}O_5$ requires *MH*, 267.1232); ν_{max}/cm^{-1} ($CHCl_3$ solution) 2930 and 1634 (C=C); δ_H (500 MHz; DMSO-d_6) 7.59 (1H, dd, J 2.6 and 1.3, 5-H furyl), 6.39 (1H, dd, J 3.3 and 2.6, 4-H furyl), 6.39 (1H, dd, J 3.3 and 1.3, 3-H furyl), 6.09 (1H, dd, J 10.4 and 1.6, 8-H), 5.82 (1H, dd, J 10.4 and 3.1, 7-H), 4.88 (1H, dd, J 3.1 and 1.6, 6-H), 4.70 (1H, dd, J 10.1 and 3.3, 2-H), 3.73 (1H, dd, J 11.4 and 4.5, 6a-H), 3.32 (3H, s, OMe), 3.22 (3H, s, OMe), 1.92 (3H, m, CH_2) and 1.69 (1H, m, CH_aH$_b$); δ_C (125 MHz; DMSO-d_6) 153.6 (2-C, furyl), 142.4 (5-C, furyl), 129.9 (8-C), 129.7 (7-C), 110.2 (3-C, furyl), 107.3 (4-C, furyl), 103.5, 95.2, 79.2, 78.6, 69.9 (OMe), 65.0 (OMe), 28.5 and 22.7; m/z (ES) 267 (MH^+, 100%).

(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionic acid (2*S*,5*S*,7*R*,10*S*)-2-(*tert*-butyldimethylsilanyloxy)-7-furan-2-yl-1,6-dioxaspiro[4.5]dec-3-en-10-yl ester 20a

Triethylamine (16 µl, 0.115 mmol), *N,N*-dimethylamino pyridine (0.35 mg, 0.0029 mmol) and (*S*)-α-methoxy-α-(trifluoro-methyl)phenyl acetyl chloride (12 µl, 0.06 mmol) were added to a stirred solution of the alcohol **17a** (10 mg, 0.029 mmol) in chloroform (0.8 ml) and the reaction mixture was stirred for 60 hours at room temperature. The reaction mixture was diluted with chloroform (2 ml), quenched with saturated sodium bicarbonate solution (0.5 ml), the layers separated and the aqueous layer was extracted with dichloromethane (2 × 1 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product. Analysis of the 500 MHz ^{1}H NMR spectrum of the crude product revealed it to be a 99 : 1 mixture of diastereoisomers. The crude product was purified by flash chromatography, eluting with 9 : 1 petrol–EtOAc to give the *(R)-Mosher's ester* **20a** (12.8 mg, 78%) as a yellow oil, R_f 0.38 (9 : 1 petrol–EtOAc); (Found: MNa^+ 591.2008; $C_{28}H_{35}O_7F_3Si$ requires *MNa*, 591.2002); $[\alpha]_D$ −2.5 (*c* 0.11 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ solution) 2930.82 (CH), 1750.17 (C=O), 1651.98, 1452.65, 1259.66, 1169.70; δ_H (500 MHz; $CDCl_3$) 7.49 (2H, m, Ph), 7.39 (3H, m, Ph), 7.36 (1H, dd, J = 1.8 and 0.9, H-5 furan), 6.30 (1H, dd, J = 3.3 and 1.8, H-4 furan), 6.26 (1H, dd, J = 3.3 and 0.6, H-3 furan), 5.80 (1H, dd, J = 5.8 and 1.0, H-3), 5.75 (1H, dd, J = 5.8 and 1.0, H-4), 5.57 (1H, t, J = 1.0, H-2), 5.20 (1H, dd, J = 11.2 and 5.0, H-7), 5.03 (1H, dd, J = 11.5 and 2.4, H-10), 3.55 (3H, s, OMe), 2.25–2.10 (3H, m, H-8^{ax+eq} and H-9^{eq}), 2.04 (1H, m, H-9^{ax}), 0.89 (9H, s, ^{t}Bu), 0.13 (3H, s, SiMe) and 0.13 (3H, s, SiMe); δ_C (125 MHz; $CDCl_3$) 165.6 (C=O ester), 153.2 (C-2 furan), 142.4 (C-5 furan), 134.9 (C-4), 132.2 (CF_3), 129.5 (C-3), 128.3 (Ph), 127.3 (Ph), 110.1 (C-4 furan), 108.5 (C-5), 107.5 (C-3 furan), 102.8 (C-2), 72.6 (C-7), 67.1 (C-10), 55.4 (OMe), 29.7 (*C*CF3), 28.4 (C-9), 25.7 (^{t}Bu), 25.2 (C-8), 18.0 (^{t}Bu), −4.2 (SiMe) and −4.7 (SiMe); m/z (ES) 591 (MNa^+, 100%).

(*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionic acid (7*S*,5*S*,7*R*,10*S*)-2-(*tert*-butyldimethylsilanyloxy)-7-furan-2-yl-1,6-dioxaspiro[4.5]dec-3-en-10-yl ester 20b

By the same general method, the alcohol **17a** (10 mg, 0.029 mmol), triethylamine (12 µl, 0.087 mmol), *N,N*-dimethylamino pyridine (0.35 mg, 0.0029 mmol) and *R*-(−)-α-methoxy-α-(trifluoro-methyl)phenyl acetyl chloride (36 µl, 0.145 mmol) gave a crude product. Analysis of the 500 MHz ^{1}H NMR spectrum of the crude product revealed it to be a 96 : 4 mixture of diastereoisomers. The crude product was purified by flash chromatography, eluting with 9 : 1 petrol–EtOAc to give the

(S)-Mosher's ester **16** (9.01 mg, 55%) as a yellow oil, R_f 0.35 (9 : 1 petrol–EtOAc); $[\alpha]_D$ −1.2 (*c* 0.1 in $CHCl_3$); (Found: MNa^+ 591.2011; $C_{28}H_{35}O_7F_3Si$ requires *MNa*, 591.2002); ν_{max}/cm^{-1} ($CHCl_3$ solution) 3369.59, 2954.62 (CH), 2929.43 (CH), 2352.48, 1750.09 (C=O), 1634.66 (C=C), 1463.65, 1257.68, 1170.78, 1121.74 and 1028.97; δ_H (500 MHz; $CDCl_3$) 7.46 (2H, m, Ph), 7.39 (3H, m, Ph), 7.36 (1H, dd, *J* = 1.8 and 0.8, H-5 furan), 6.30 (1H, dd, *J* = 3.2 and 1.8, H-4 furan), 6.25 (1H, d, *J* = 3.2, H-3 furan), 5.93 (1H, dd, *J* = 5.8 and 0.9, H-4), 5.90 (1H, dd, *J* = 5.8 and 1.0, H-3), 5.77 (1H, t, *J* = 1.0, H-2), 5.19 (1H, dd, *J* = 10.1 and 5.7, H-7), 5.03 (1H, dd, *J* = 11.1 and 2.9, H-10), 3.45 (3H, d, *J* = 1.0, OMe), 2.2–2.1 (3H, m, H-8^{ax+eq} and H-9^{eq}), 1.99 (1H, m, H-9^{ax}), 0.91 (9H, s, ^{t}Bu), 0.15 (3H, s, SiMe) and 0.14 (3H, s, SiMe); δ_C (125 MHz; $CDCl_3$) 165.8 (C=O ester), 153.2 (C-2 furan), 142.4 (C-5 furan), 134.9 (C-4), 131.9 (CF_3), 130.2 (C-3), 129.6 (Ph), 128.4 (Ph), 127.6 (Ph), 110.1 (C-4 furan), 108.6 (C-5), 107.5 (C-3 furan), 102.8 (C-2), 73.1 (C-7), 67.2 (C-10), 55.2 (OMe), 28.3 (C-8), 25.7 (^{t}Bu), 24.9 (C-9), 18.0 (^{t}Bu), −4.1 (SiMe) and −4.7 (SiMe); *m*/*z* (ES) 591 (MNa^+, 100%).

(3*R**,4*S**)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1,6-difuran-2-ylhexane-1,6-diol 23

n-Butyl lithium (12.5 ml of 1.3 M solution in hexanes, 16.3 mmol) was added dropwise to furan (1.5 ml, 20.4 mmol) in dry THF (20 ml) at 0 °C under nitrogen. The solution was stirred at 0 °C for 30 min before being added dropwise by cannula to a solution of (3*R**, 4*S**)-3,4-bis(*tert*-butyldimethylsilyloxy)hexanedial[22] (1.1 g, 6.8 mmol) in dry THF at −78 °C under nitrogen. The reaction mixture was stirred at −78 °C for 3 h before being quenched with saturated aqueous ammonium chloride solution (20 ml) and the reaction mixture allowed to warm to room temperature. The two layers were separated and the aqueous layer extracted with EtOAc (3 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford the *diol* **23** (1.4 g, 88%) as a mixture of diastereoisomers. Analysis of the crude reaction mixture by 300 MHz ^{1}H NMR spectroscopy revealed that ^{1,3}*syn*,*anti*,^{1,3}*syn*-**23** was present and was spectroscopically identical to that obtained subsequently. The crude reaction mixture was used in the next reaction without further purification.

(3*R**,4*S**)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1,6-difuran-2-ylhexane-1,6-dione 24

Manganese dioxide (87 g, 100 mmol) was dried by heating in the furnace overnight before being transferred to a dry round bottom flask and allowed to cool to room temperature under nitrogen. Dry dichloromethane (30 ml) and the diol **23** (500 mg, 1.0 mmol) were added and the reaction mixture was refluxed for 24 h, with vigorous stirring, and then allowed to cool to room temperature. The dichloromethane was removed under reduced pressure and the crude residue taken up in EtOAc (30 ml). The reaction mixture was filtered through Celite, washing with EtOAc, and the filtrate evaporated to leave the *dione* **24** (467 mg, 94%) as colourless prisms, mp 88–90 °C; R_f 0.50 (15 : 85 EtOAc–petrol); (Found: MH^+ 507.2596; $C_{26}H_{43}O_6Si_2$ requires *MH*, 507.2598); ν_{max}/cm^{-1} (nujol mull) 2929, 1676, 1569, 1470, 1254 and 1087; δ_H (300 MHz; $CDCl_3$) 7.46 (2H, dd, *J* 1.8 and 0.8, furyl 5-H), 7.07 (2H, dd, *J* 3.6 and 0.8, furyl 3-H), 6.41 (2H, dd, *J* 3.6 and 1.8, furyl 4-H), 4.26 (2H, dd, *J* 7.2 and 4.2, 3-H and 4-H), 2.98 (2H, dd, ^2J 15.5 and *J* 7.9, 2-H_A and 5-H_A), 2.70 (2H, dd, ^2J 15.5 and *J* 4.2, 2-H_B and 5-H_B), 0.68 (18H, s, 2 × ^{t}Bu), 0.00 (6H, s, 2 × Me–Si) and −0.17 (6H, s, 2 × Me–Si); δ_C 188.1 (1-C and 6-C), 153.5 (furyl 2-C), 147.0 (furyl 5-C), 118.2 (furyl), 112.71 (furyl), 73.8 (3-C and 4-C), 42.6 (2-C and 5-C), 26.2 (2 × ^{t}Bu), −3.8 (2 × Me–Si) and −4.8 (2 × Me–Si); *m*/*z* (ES) 507.3 (100%, MH^+), 375 (73, MH^+–OTBS), 357 (93) and 243 (48, MH^+ −2 OTBS).

(1*R**,3*S**,4*R**,6*S**)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1,6-difuran-2-ylhexane-1,6-diol ^{1,3}*syn*,*anti*,^{1,3}*syn*-23

Di-*iso*-butyl aluminium hydride (1.3 ml of a 1 M solution in toluene, 1.3 mmol) was added to a stirred solution of the dione **24** (300 mg, 0.6 mmol) in toluene (5 ml) at −78 °C under nitrogen. The reaction mixture was stirred at −78 °C for 2 h before being quenched with methanol (5 ml). The reaction mixture was allowed to warm to room temperature and then saturated aqueous sodium potassium tartrate solution (15 ml) was added. The gelatinous mixture was stirred vigorously until two layers were formed (~30 min). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Analysis of the crude product by 300 MHz ^{1}H NMR spectroscopy revealed a 85 : 15 mixture of diastereoisomers. Purification by flash column chromatography, eluting with 15 : 85 EtOAc–petrol, afforded the *diol* ^{1,3}*syn*,*anti*,^{1,3}*syn*-**23** (239 mg, 78%) as a colourless oil, R_f 0.40 (15 : 85 EtOAc–petrol); ν_{max}/cm^{-1} ($CHCl_3$ solution): 3391 (OH), 1644, 1472, 1255, 1009 and 836; δ_H (300 MHz; $CDCl_3$) 7.26 (2H, dd, *J* 1.8 and 0.8, furyl 5-H), 6.23 (2H, dd, *J* 3.3 and 1.8, furyl 4-H), 6.14 (2H, dd, *J* 3.3 and 0.8, furyl 3-H) 4.77 (2H, t, *J* 6.5, 1-H and 6-H), 3.76 (2H, app t, *J* 6.5, 3-H and 4-H), 1.98 (4H, m, 2-H and 5-H), 0.82 (18H, s, 2 × ^{t}Bu), 0.00 (6H, s, 2 × MeSi) and −0.10 (6H, s, 2 × MeSi); δ_C 157.1 (furyl 2-C), 142.4 (furyl 5-C), 110.6 (furyl), 106.0 (furyl), 74.0 (1-C and 6-C), 64.9 (3-C and 4-C), 39.4 (2-C and 5-C), 26.3 (2 × ^{t}Bu), −3.6 (2 × MeSi) and −4.7 (2 × MeSi); *m*/*z* (ES) 533.5 (94%, MNa^+), 361.3 (100%).

Also obtained was the *diol* ^{1,3}*syn*,*anti*,^{1,3}*anti*-**23** (43 mg, 14%) as a colourless oil, R_f 0.38 (15 : 85 EtOAc–petrol); ν_{max}/cm^{-1} ($CHCl_3$ solution): 3368 (OH), 1643, 1472, 1254, 1069 and 836; δ_H (300 MHz; $CDCl_3$) 7.26 (2H, d, *J* 1.8, furyl 5-H), 6.23 (2H, dd, *J* 3.3 and 1.8, furyl 4-H), 6.14 (1H, m, 6-furyl 5-H), 6.12 (1H, m, 1-furyl 5-H), 4.82 (1H, m, 1-H), 4.77 (1H, t, *J* 6.5, 6-H), 3.98 (1H, m, 3-H), 3.76 (1H, app t, *J* 6.5, 4-H), 2.00 (4H, m, 2-H and 5-H), 0.82 (18H, s, *t*-Bu), 0.00 (6H, s, MeSi) and −0.10 (6H, s, MeSi); δ_C 157.1 (furyl 2-C), 142.4 and 142.2 (furyl 5-C), 110.6 (furyl C), 110.5 (furyl C), 106.2 (furyl C), 106.1 (furyl C), 74.9 and 74.0 (1-C and 6-C), 64.6 (3-C and 4-C), 39.4 (2-C and 5-C), 26.5 (*t*-Bu), −3.43 (SiMe), −4.54 (SiMe), −4.77 (SiMe).

(1*R**,3*S**,4*R**,6*S**)-1,6-Difuran-2-ylhexane-1,3,4,6-tetraol 25

Tetra-*n*-butylammonium fluoride (1.0 ml of a 1 M solution in tetrahydrofuran, 1.0 mmol) was added to a stirred solution of the diol ^{1,3}*syn*,*anti*,^{1,3}*syn*-**23** (160 mg, 0.31 mmol) in THF (3 ml) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 12 h before the solvent was evaporated under reduced pressure and the crude residue pre-absorbed onto silica gel. Purification by flash column chromatography, eluting with EtOAc, afforded the *tetraol* **25** (76 mg, 86%) as colourless prisms, mp 92–94 °C; R_f 0.34 (EtOAc); (Found: MNa^+ 305.1009; $C_{14}H_{18}O_6Na$ requires *MNa*, 305.1001); ν_{max}/cm^{-1} (nujol mull) 3412 (OH), 2927, 1649, 1440, 1148 and 1068; δ_H (300 MHz; MeOD) 7.35 (2H, dd, *J* 1.8 and 0.8, furyl 5-H), 6.27 (2H, dd, *J* 3.3 and 1.8, furyl 3-H), 6.20 (2H, dd, *J* 3.3 and 0.8, furyl 4-H), 4.77 (2H, dd, *J* 6.4 and 1.8, 1-H and 6-H), 3.25 (2H, m, 3-H and 4-H), 2.06 (2H, m, 2-H_A and 5-H_A) and 1.79 (2H, m, 2-H_B and 5-H_B); δ_C 158.1 (furyl 2-C), 143.6 (furyl 5-C), 111.5 (furyl C), 107.9 (furyl C), 74.2 (1-C and 6-C), 67.0 (3-C and 4-C), 39.6 (2-C and 5-C); *m*/*z* (ES) 304.7 (100%, MNa^+).

(4*R**,6*S**,4′*S**,6′*R**)-2,2,2′,2′-Tetra-*tert*-butyl-6,6′-difuran-2-yl[4,4′]bi{[1,3,2]dioxasilinane} 26

Di-*tert*-butylsilyl ditriflate (198 μl, 0.54 mmol) was added to a stirred solution of the *tetraol* **25** (50 mg, 0.18 mmol) and pyridine (100 μl, 1.2 mmol) in dry dichloromethane (1.5 ml) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C

for 2 h before being quenched with triethylamine (0.2 ml). The reaction mixture was evaporated under reduced pressure and the crude residue pre-absorbed onto silica gel. Purification by flash column chromatography, eluting with 5 : 95 EtOAc–petrol, afforded the *silylated tetraol* **26** (83 mg, 83%) as a colourless oil, R_f 0.58 (5 : 95 EtOAc–petrol); ν_{max}/cm^{-1} ($CHCl_3$ solution) 2933, 2859, 1471, 1386, 1148, 1114 and 1012; δ_H (500 MHz; $CDCl_3$) 7.37 (2H, d, *J* 1.8, furyl 5-H), 6.34 (2H, dd, *J* 3.2 and 1.8, furyl 3-H), 6.25 (2H, d, *J* 3.2, furyl 4-H), 5.17 (2H, dd, *J* 11.7 and 2.3, 6-H and 6′-H), 3.94 (2H, d, *J* 11.7, 4-H and 4′-H), 2.29 (2H, app d *J* 13.9, 5-H_A and 5′-H_A), 1.89 (2H, app dt *J* 13.9 and 11.6, 5-H_B and 5′-H_B), 1.04 (9H, ′Bu) and 1.01 (9H, ′Bu); δ_C 157.6 (furyl 2-C), 142.0 (furyl 5-C), 110.5 (furyl C), 105.4 (furyl C), 77.7 (C-O), 70.3 (C-O), 37.3 (2-C and 5-C), 27.9 and 27.5 (′Bu). Careful analysis of the signals corresponding to 4-H and 6-H revealed both of these protons to be axial.

(2*R**)-2-{(2*S**,3*R**)-2,3-Bis(*tert*-butyldimethylsilyloxy)-4-[(*S**)-3-oxo-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl]butyl}-6-methoxy-2,3-dihydro-6*H*-pyran-3-one 27

tert-Butylhydroperoxide (0.5 ml, 2.6 mmol, 5 M solution in decanes), was added to a stirred solution of the diol ^{1,3}*syn*, *anti*,^{1,3}*syn*-**23** (400 mg, 0.8 mmol) and vanadyl acetylacetonate (5 mg) in dichloromethane (10 ml) at room temperature under nitrogen. The solution was stirred for 8 h before being quenched with a 1 : 1 saturated aqueous solution of ferrous sulfate–tartaric acid (10 ml). The two layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford a crude product. Dichloromethane (10 ml) and trimethyl orthoformate (205 μl, 193 mmol) were added followed by boron trifluoride diethyletherate complex (10 μl, 80 μmol, 10 mol%). The reaction mixture was stirred for 10 min under nitrogen, quenched with saturated aqueous sodium bicarbonate solution (10 ml) and the two layers separated. The aqueous layer was extracted with dichloromethane (2 × 10 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated to afford the *diacetal* **27** (416 mg, 93%; 61 : 39 mixture of anomers) as a colourless oil, R_f 0.53 (20 : 80 EtOAc–petrol); (Found: MH^+ 571.3120; $C_{28}H_{51}O_8Si_2$ requires *MH*, 571.3123); ν_{max}/cm^{-1} ($CHCl_3$ solution) 2930, 2857, 1698 (C=O), 1472, 1256, 1101 and 1051; δ_H (300 MHz; $CDCl_3$) 6.76 (2H, m, 5-H^{min}), 6.72 (2H, dd, *J* 10.2 and 3.5, 5-H^{maj}), 6.05 (2H, m, 4-H^{min}), 5.96 (2H, m, 4-H^{maj}), 5.13 (2H, app s, 6-H^{min}), 4.96 (2H, d, *J* 3.5, 6-H^{maj}), 4.52 (2H, m, 2-H^{min}), 4.17 (2H, m, 2-H^{maj}), 3.85–4.0 (4H, m, 2 × $CHOSi^{maj+min}$), 3.44 (6H, s, 2 × OCH_3^{min}), 3.41 (6H, s, 2 × OCH_3^{maj}), 1.95–2.22 (4H, m, CH_AH_B), 1.63–1.81 (4H, m, CH_AH_B), 0.78 (9H, s, 2 × ′Bu^{min}), 0.77 (9H, s, 2 × ′Bu^{maj}), 0.00 (3H, s, $SiCH_3^{maj}$), −0.01 (3H, s, $SiCH_3^{maj}$), −0.04 (3H, s, $SiCH_3^{min}$), −0.05 (3H, s, $SiCH_3^{min}$); δ_C 198.0 (3-C^{min}), 197.8 (3-C^{maj}), 146.7 (5-C^{min}), 143.3 (5-C^{maj}), 129.1 (4-C^{min}), 128.1 (4-C^{min}), 97.2 (6-C^{min}), 94.6 (6-C^{maj}), 76.4 (C^{maj}), 73.3 (C^{maj}), 71.1 (C^{min}), 57.1 (C^{maj}), 56.6 (C^{min}), 36.1 (C^{min}), 34.2 (C^{maj}) 26.4 (2 × ′Bu^{maj}), 26.3 (2 × ′Bu^{min}), −3.5 (Si–CH_3^{min}), −3.7 (Si–CH_3^{min}), −4.3 (Si–CH_3^{maj}) and −4.5 (Si–CH_3^{maj}); *m*/*z* (ES) 571.4 (24%, MH^+), 539.3 (100%).

(2*R**)-2-{(2*S**,3*R**)-2,3-Bis(*tert*-butyldimethylsilyloxy)-4-[(*S**)-3-oxo-6-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]butyl}-6-methoxy-2,3,4,5-tetrahydro-6*H*-pyran-3-one 28

Palladium on charcoal (10%, 10 mg) was added to a stirred solution of the dipyranone **27** (100 mg, 0.18 mmol) in ethyl acetate (1.5 ml). The suspension was treated with hydrogen at room temperature and atmospheric pressure. Hydrogenolysis was followed by TLC (20 : 80 EtOAc–petrol) and was found to be complete after 1 h. The reaction mixture was filtered through a pad of silica, eluting with EtOAc. The filtrate was evaporated under reduced pressure to give the *diacetal* **28** (91 mg, 97%; 61 : 39 mixture of anomers) as a colourless oil, R_f 0.56 (20 : 80 EtOAc–petrol); (Found: MNa^+ 597.3260; $C_{28}H_{54}O_8NaSi_2$ requires *MNa*, 597.3255); ν_{max}/cm^{-1} ($CHCl_3$ solution) 2930, 2857, 1728 (C=O), 1472, 1256 and 1060; δ_H (300 MHz; $CDCl_3$) 4.78 (2H, m, 6-H^{maj}), 4.72 (2H, m, 6-H^{min}), 4.25 (2H, m, 2-H^{maj}), 4.10 (2H, m, 2-H^{min}), 3.80–4.00 (4H, m, 2 × $CHOSi^{maj+min}$), 3.39 (6H, s, 2 × OMe^{min}), 3.34 (6H, s, 2 × OMe^{maj}), 1.50–2.50 (12H, m, 2 × $CH_2^{maj+min}$), 0.80 (18H, s, 2 × ′Bu^{min}), 0.79 (18H, s, 2 × ′Bu^{maj}), −0.01 (3H, s, $SiMe^{maj}$), −0.02 (3H, s, $SiMe^{min}$), −0.05 (3H, s, $SiMe^{maj}$) and −0.06 ($SiMe^{min}$); δ_C 210.5 (3-C^{maj}), 208.9 (3-C^{min}), 99.8 (6-C^{min}), 97.8 (6-C^{maj}), 72.8 (C^{maj}), 72.7 (C^{min}), 71.4 (C^{maj}), 71.0 (C^{min}), 56.1 (C^{min}), 55.4 (C^{maj}), 34.3 (C^{min}), 34.2 (C^{maj}), 33.3 (C^{maj}), 33.0 (C^{min}), 29.7 (C^{min}), 29.5 (C^{maj}), 26.0 (2 × ′Bu^{maj}), 25.8 (2 × ′Bu^{min}), −4.0 (Si–Me^{min}), −4.1 (Si–Me^{maj}), −4.8 (Si–Me^{min}) and −5.0 (Si–Me^{maj}); *m*/*z* (ES) 575.4 (92 %, MH^+), 491.3 (94), 443.3 (98, MH^+–OTBS) and 411.2 (100).

(2*R**,3a*S**,5*R**,7a*S**,2′*S**,3′a*R**,5′*S**,7′a*S**)-5,7a,5′,7′a-Tetramethoxydodecahydro[2,2′]bi{furano[3,2-*b*]pyran} 13

p-Toluenesulfonic acid (1.3 mg, 9 μmol) was added to a solution of the diacetal **28** (50 mg, 87 μmol) in methanol (3 ml). The solution was stirred at room temperature for 84 h before being quenched with saturated aqueous ammonium chloride solution (2 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 5 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to afford the *tetraacetal* **13** (20 mg, 86%) as colourless plates, R_f 0.92 (EtOAc); (Found: MNa^+ 397.1830; $C_{18}H_{30}O_8Na$ requires *MNa*, 397.1838); ν_{max}/cm^{-1} ($CHCl_3$ solution) 2936, 1440, 1221, 1116, 1058 and 1019; δ_H (500 MHz; $CDCl_3$) 4.65 (2H, m, 5-H and 5′H), 4.18 (2H, m, 2-H and 2′-H), 4.00 (2H, m, 3a-H and 3a′H), 3.39 (6H, 2 × OCH_3), 3.21 (6H, 2 × OCH_3), 2.16–2.26 (2H, m, 3-H_A and 3′-H_A), 2.03–2.08 (4H, m, 3-H_B, 3′-H_B, 7-H_A and 7′-H_A), 1.87–1.93 (2H, m, 7-H_B and 7′H_B) and 1.71–1.77 (4H, m, 6-H and 6′-H); δ_C 104.2 (7a-C and 7a′-C), 97.5 (5-C and 5′-C), 83.3 (3a-C and 3a′-C), 74.4 (7a-C and 7a′-C), 54.9 (2 × OCH_3), 47.4 (2 × OCH_3), 35.86 (3-C and 3′-C), 26.5 (6-C and 6′-C) and 22.3 (7-C and 7′-C); *m*/*z* (ES) 397.3 (20 %, MNa^+), 343.2 (73, M^+–OCH_3), 311.2 (100), 279 (64). The relative configuration of the tetraacetal **13** was confirmed by X-ray crystallographic analysis.

Crystal structure determination of the tetraacetal 13‡

Crystal data. $C_{18}H_{30}O_8$, *M* = 374.42, Monoclinic, *a* = 17.7588(10) Å, *a* = 90°, *b* = 7.8904(4) Å, *β* = 91.161(3)°, *c* = 13.1044(7) Å, *γ* = 90°, *U* = 1835.86(17) Å^3, *T* = 150 K, space group *C*2/*c*, *Z* = 4, *μ*(Mo–K_α) = 0.106 mm^{-1}, 7982 reflections measured, 1795 unique (R_{int} = 0.1062) which were used in all calculations. The final *wR* (F^2) was 0.1395 (all data).

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